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09/673,884	10/23/2000	Kiyozo Asada	1422-443P	6983

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
03/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	09/673,884	ASADA ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,18,31,34,36,38,40-42 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18,31,34,36,38,40-42 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an after-final amendment filed February 6, 2008. Claims 16, 18, 31, 34, 36 and 38-45 were previously pending. Applicants cancelled claims 39, 43 and 44, amended claims 18, 31 and 36, and added new claims 46 and 47. Claims 16, 18, 31, 34, 36, 38, 40-42 and 45-47 are pending and will be examined.

2. Applicants' amendments overcame all of the previously pending rejections.

3. This office action is made non-final because of new grounds for rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 16, 18, 31, 34, 36, 38, 40-42 and 45-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA synthesis reaction composition comprising sulfated-fucose-containg polysaccharides (SFCPs) F and U at concentrations in the range of 0.02 to 5 ng/μL for amplification of DNA fragments up to 15 kb in length, or a reaction composition comprising sodium alginate in the concentration range of 5-100 ng/μL for amplification of DNA fragments up to 12 kb in length, does not reasonably provide enablement for DNA synthesis reaction compositions comprising hyaluronic acid, polyglutamic acids, polyacrylic acids, polystyrene sulfates, dermatan sulfate or polyvinyl sulfates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to compositions and kits for performing PCR where heparin or a number of other acidic macromolecular substances is added to enhance PCR. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass the use of reaction mixtures for PCR amplification comprising sulfated-fucose-containg polysaccharides, alginic acid, hyaluronic acid, polyglutamic acids, polyacrylic acids, polystyrene sulfates, dermatan sulfate or polyvinyl sulfates or their salts to enhance PCR. The claims broadly encompass the use of the reaction mixtures in PCR samples derived from any cell type, ranging from plants to animals to soil microorganisms.

Working Examples

The specification has working examples showing enhancement of PCR amplification by the following substances: sulfated-fucose-containing polysaccharides F and U concentrations in the range of 0.02 to 5 ng/μL for amplification of DNA fragments up to 15 kb in length, sodium alginate in the concentration range of 5-100 ng/μL for amplification of DNA fragments up to 12 kb in

length, whereas all other acidic substances (dermatan sulfate, hyaluronic acid, polyglutamic acids, polyacrylic acids, polyvinyl sulfates, polystyrene sulfates) were tested only at one or up to three concentrations with a single DNA polymerase (KOD) and only with a single length of the amplified fragments (either 1 kb or 10 kb).

Guidance in the Specification.

The specification teaches that acidic macromolecular compounds can be used to enhance amplification, but shows that only the following substances actually do within the range of concentrations tested: sulfated-fucose-containing polysaccharides and sodium alginate, since these two substances were tested at a range of concentrations, different polymerases and different lengths of amplified fragments.

The unpredictability of the art and the state of the prior art

Except for the polysaccharides and sodium alginate cited above, Applicants did not show that any other polyionic substances enhance PCR reactions.

Peters (U.S. 2003/0092135; cited in the previous office action) teaches that polyanions themselves are inhibitory to PCR, noting "Acid polyanionic polysaccharides have been characterized as the major PCR inhibitor in plant DNA isolations (Demeke et al., 1992; cited in the previous office action), whereas sulfated polysaccharides, such as dextran sulfate and heparin were identified as potent PCR inhibitors contaminating DNA preparations from blood cells (Al-Soud et al., 2001; cited in the previous office action). Sulfated polysaccharides in particular show a broad spectrum of inhibition against a variety of DNA-modifying enzymes including Polynucleotide Kinase (Wu et al., 1971; cited in the previous office action), restriction endonucleases (Do et al., 1991; cited in the previous office action) and retroviral reverse transcriptases (Moelling et al., 1989; cited in the previous office action). Although the inhibitory effect of polyanions and sulfated

polysaccharides in particular has been studied for many years, the exact mechanism is not known (see paragraph 21)."

Therefore, the great weight of both the prior and post filing date art, in both the patent and non-patent literature, teach that addition of polyionic compounds do not enhance PCR amplification as claimed in this application. The examiner did not find a single prior art patent or non-patent literature reference that yielded a different conclusion. Therefore, one of ordinary skill in the art would not conclude that any polyionic acidic polymers can be used to enhance PCR amplification unless experimentally determined.

Quantity of Experimentation

The quantity of experimentation in this area is large since there is significant variability in the efficacy of steps taken to enhance PCR. This experimentation must take into account variables that depend upon the environment in which the DNA is found as well as the age of the DNA sample and the source of the DNA sample. Different inhibitors are present in ancient DNA samples than in modern DNA samples and different PCR inhibitors are present in plants than are present in blood samples or soil samples. Each of these unique sample types would require independent experimentation and screening in order to determine the efficacy and ability of specific compounds to enhance PCR. Such efforts are inventive, unpredictable and difficult undertakings, as shown by the many patents such as Harvey et al. (U.S. Patent 6,168,922; cited in the previous office action), which discusses removal of PCR inhibitors. The efficacy of any particular compound to enhance PCR of any particular sample would need to be demonstrated. Further, as the efficacy of amplification depends on the amplification conditions, i.e., number of PCR cycles, length and temperature of cycles, ionic strength of buffer, amount of target nucleic acid, primer concentration, etc., optimization of these factors for all possible concentrations of the compounds claimed would

definitely not constitute routine experimentation. Therefore achieving PCR reaction enhancement using claimed substances in any range of concentration would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching of prior art documents that polyanions are PCR inhibitors, support the conclusion of undue experimentation. The specification provides one with little written description or guidance that leads one to overcome the art recognized fact that polyanions are themselves PCR inhibitors. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of working examples commensurate in scope with the claims and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite over the recitation of "said DNA polymerase is thermostable". Claim 38 depends from claim 36, which is drawn to two or more kinds of DNA polymerases, therefore it is not clear which one of the polymerases is thermostable.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Al-Soud et al. (Applied Env. Microbiol., vol. 64, pp. 3748-3753, October 1998; cited in the previous office action), as evidenced by Wikipedia ("Heparan Sulfate", April 21, 2007; cited in the previous office action) and Stratagene catalog (page 39, 1988; cited in a previous office action).

A) Regarding claims 36 and 38, Al-Soud et al. teach a composition comprising a DNA polymerase or two DNA polymerases, and components necessary for DNA synthesis using a polymerase, as well as diluted minced pork meat (page 3749, paragraphs 2-5). Al-Soud et al. do not specifically teach heparan sulfate. However, as evidenced by Wikipedia, heparan sulfate is present in all animal tissues. Therefore, by teaching polymerization reaction with meat solutions Al-Soud et al. inherently teach polymerization in the presence of heparan sulfate. Al-Soud et al. teach Taq DNA polymerase (polymerase without 3'-> 5' exonuclease activity) and Pyrococcus-derived (Pwo) polymerase (polymerase with 3'-> 5' exonuclease activity) and both of these polymerases being thermostable (page 3749, second paragraph; Table 1, 2).

B) Al-Soud et al. teach the reaction composition, but they do not teach kits.

C) Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the compositions of Al-Soud al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantitites of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantitites you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
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Primary Examiner, Art Unit 1637

February 28, 2008